REMARKS

Claims 27-30, 33-40, 42-54, 59-68, 73-75, 84-85 and 90-104 are pending in the application. In the Office Action mailed December 16, 2004, claims 27-30, 33-40, 42-54, 59-68, 73-75, 84-85 and 90-104 are rejected. In the present Amendment, claims 27, 67, 91 and 93 have been amended to clarify the invention. Upon entry of the above-made amendments, claims 27, 29-30, 33-40, 42-54, 59-67, 73-75, 84-85 and 90-104 will be pending in the application.

Claim 27 has been amended to clarify that the probe comprises a *predetermined nucleotide base sequence* that is complementary to at least a hybridizable portion of the target sequence (emphasis added). Support for the amendment is found in the specification at, e.g., page 18, lines 5-6; page 22, lines 24-26; page 22, line 35 through page 23, line 14; page 23, line 35; page 24, line 20 through page 25, line 22; and the Example beginning on page 46.

Claims 67, 91 and 93 have been amended to clarify that the probe comprises a *different predetermined nucleotide base sequence* that is complementary to at least a hybridizable portion of the target sequence (emphasis added). Support for the amendment is found in the specification at, e.g., page 18, lines 5-6; page 22, lines 24-26; page 22, line 35 through page 23, line 14; page 23, line 35; page 24, line 20 through page 25, line 22; page 26, lines 18-31; and the Example beginning on page 46.

Claims 27, 67, 91 and 93 have also been amended to make the language clearer.

No new matter has been added by these amendments. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

APPLICANT'S INTERVIEW SUMMARY

Applicant thanks Primary Examiner Betty J. Forman for the courtesies extended during the telephonic interview on March 15, 2005 (hereinafter "the Interview") with Adriane M. Antler, R. Douglas Bradley, and Weining Wang. During the interview, Ms. Antler proposed to amend the independent claims 27, 67, 91 and 93 to clarify that the probe comprises a predetermined nucleotide base sequence, i.e., a sequence whose base sequence has been determined and is known, that is complementary to at least a portion of a target nucleotide sequence. Ms. Antler pointed out that Lo et al., U.S. Patent No. 4,900,659 ("Lo"),

does not teach that any of its probes has a predetermined base sequence. Nor does Lo teaches determination of the base sequences of its probes. The Examiner indicated that recitation in the claims that the probe comprises a predetermined or known nucleotide base sequence would overcome the rejection under 35 U.S.C. 102(b) based on Lo. However, the Examiner indicated that the proposed amendments would not be entered. Ms. Antler thus proposed to file a Request for Continued Examination (RCE) with the Amendment. The Examiner further indicated that she wished to consider whether the combination of Lo and Lockhart would make such amended claims obvious.

THE REJECTION UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 27-30, 33-36, 38, 40, 43-54, 59-60, 64-65, 67-68, 73, 90-91, 93 and 95-104 are rejected under 35 U.S.C. § 102(b) as being anticipated by Lo et al., U.S. Patent No. 4,900,659 ("Lo"). The Examiner contends that the presently claimed methods are not limited to probes comprising a predetermined nucleotide base sequence, and therefore are anticipated by Lo. Applicant respectfully disagrees with the Examiner for the reasons presented below.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.,* 52. F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

To make the claimed invention clear, Applicant has amended claims 27, 67, 91 and 93 to recite that the probe in the presently claimed invention comprises a predetermined nucleotide *base* sequence that is complementary to at least a hybridizable portion of said target nucleotide sequence. The presently claimed invention thus relates to methods for evaluating a binding property of a polynucleotide probe to a target nucleotide sequence, where the probe has a known nucleotide sequence, i.e., a predetermined nucleotide base sequence, that is complementary to at least a hybridizable portion of the target nucleotide sequence. The claimed methods make use of the hybridization levels of the probe to certain samples, i.e., a first sample comprising polynucleotide molecules *comprising* the target nucleotide sequence of the probe, and a second sample comprising polynucleotide molecules having other sequences. Thus, the methods of the invention evaluate how the probe binds to

its complementary sequence versus to other, partially complementary or non-complementary, sequences. It is well-known that even though a polynucleotide probe having a predetermined, known base sequence is expected to bind its target sequence, the probe may also bind such partially complementary or non-complementary sequences to various degrees. Such cross-hybridization may be more significant for some probes while less significant for other probes. The claimed methods allow evaluation of a probe for its binding property with respect to target hybridization versus cross-hybridization.

In contrast, Lo's method is to identify, among different probes having unknown sequences, those that exhibit specificity to *N. gonorrhoeae* but not to *N. meningitidis*, wherein the genomic sequences of neither strain are taught by Lo. The probes of Lo are fragments from chromosomal DNA. In Lo, *N. gonorrhoeae* chromosomal DNA is digested into fragments (see, Lo, col. 5, Section A). Each of the fragments is inserted into a vector to form a recombinant molecule (see, Lo, col. 6, Section B). The recombinant molecule is transformed into a suitable host, e.g., *E. coli* (Lo, col. 6, Sections C and D). The recombinant molecules are amplified (Lo, col. 7, Section E). The recombinant molecules are then screened against *N. gonorrhoeae* and *N. meningitidis* chromosomal DNAs to identified those sequences that are specific for *N. gonorrhoeae* (Lo, col. 8, Section F). The screening is carried out using test dots each consisting of denatured purified chromosomal DNA from either *N. gonorrhoeae* or *N. meningitidis*, i.e., each test dot consists of chromosomal DNA from one strain of *N. gonorrhoeae* or *N. meningitidis* (Lo, col. 8, lines 13-19). A recombinant molecule is identified if the ratio of its hybridization amount to a test dot containing fragments of chromosomal DNA of a strain of *N. gonorrhoeae* and its hybridization amount to a test dot containing fragments of chromosomal DNA of a strain of *N. meningitidis* is greater than a preset value, e.g., 5 (Lo, col. 10, lines 55-67). Thus, Lo does not teach what the base sequences of its nucleic acid probes are. Nor does Lo teach determination of the base sequence of any of its nucleic acid probes. Therefore, Lo does not teach a method of evaluating a binding property of a probe that comprises a *predetermined nucleotide base sequence.* Thus, Lo does not anticipate the presently claimed invention.

Additionally with respect to claims 27 and 67, Lo does not teach, expressly or inherently, that its *N. gonorrhoeae* test dots contain at least 75% polynucleotide molecules that comprise a target sequence to which a predetermined nucleotide sequence of the fragment is hybridizable. In the randomly generated sheared fragments of Lo that make up

the test dot, the sample would not necessarily contain at least 75% polynucleotide molecules that comprise a particular target sequence.

Applicant also respectfully points out that claims 36, 38, 40, 43-54, 91 and 95-104 each also contains a limitation regarding a particular relation between the sequence composition of the first sample and the composition of the second sample. For example, claims 36 and 91 specifies that the second sample does not comprise the target sequence, claim 38 specifies that the second sample comprises both polynucleotide molecules that comprises the target sequence and polynucleotide molecules that do not comprise the target sequence, whereas claims 43-54 and 95-104 require that the first sample further comprises polynucleotide molecules that do not comprise the target nucleotide sequence, and the second sample comprises: (i) polynucleotide molecules comprising the target nucleotide sequence, and (ii) a plurality of different polynucleotide molecules, each different polynucleotide molecule comprising a different nucleotide sequence and not comprising the target nucleotide sequence, where the amount of polynucleotide molecules in the first sample comprising the target nucleotide sequence and the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence differ by a specified amount. Lo does not teach such particular relationships between its first and second samples.

Thus, Applicant respectfully submits that Lo does not anticipate claims 27, 29-30, 33-36, 38, 40, 43-54, 59-60, 64-65, 67-67, 73, 90-91, 93 and 95-104, and that the rejection of these claims under 35 U.S.C. § 102(b) based on Lo should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 37, 39, 42, 92 and 94 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lo et al., U.S. Patent No. 4,900,659 ("Lo"). Claims 61-63, 66, 74-75, and 84-85 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lo in view of Lockhart et al., U.S. Patent No. 6,344,316 ("Lockhart"). In the Office Action mailed December 16, 2004, the Examiner reiterate and maintain the rejections of these claims. Applicant respectfully disagrees with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the

invention was made. *Graham v. Deere*, 383, U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Rouffet, 149 F.3d 1350* (Fed. Cir. 1998).

With respect to claims 37, 39, 42, 92 and 94, Applicant first respectfully submits that, as discussed above, Lo does not teach or suggest probes having predetermined nucleotide base sequences. Nor does Lo teach or suggest known sequence compositions in its samples. Thus, Lo does not teach or suggest evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide base sequence.

Applicant also respectfully points out that claims 37, 39, 42, 92 and 94 each further contain a limitation regarding a particular relation between the first sample and the second sample. Claims 37, 39, 42, 92 and 94 specify that the target polynucleotide sequence in the first sample is a sequence from a gene or gene transcript of a cell or organism, whereas claims 37, 42, and 92 specify that the second sample comprises a polynucleotide sample from a deletion mutant of the cell or organism, wherein the deletion mutant of the cell or organism does not express the gene or gene transcript; claims 39 and 94 specify that the second sample comprises a polynucleotide sample from a wild-type strain of the cell or organism. Lo does not teach or suggest a method of evaluating a binding property of probes having predetermined nucleotide base sequences using a pair of samples having such particular relations. The Examiner contends that because Lo teaches a method for screening nucleotide sequences using closely related species, Lo suggests a method of screening using a wild-type and a deletion mutant. Applicant respectfully points out that merely teaching screening with closely related species does not teach or suggest use of a deletion mutant or a wild-type strain since "closely related species" could be referring to many other types of relationships, e.g., phylogenetic relationships.

With respect to claims 61-63, 66, 74-75, 84-85, the Examiner contends that although Lo does not teach that the probes are fixed on an array in which different probes are attached to different locations and does not teach differentially labeling polynucleotides with

fluorescent labels, Lockhart teaches fixing probes on an array and differentially labeling polynucleotides with fluorescent labels thereby providing teachings that are missing in Lo.

Lo has been discussed above. Lockhart teaches methods for identifying differences in nucleic acid abundances (e.g., expression levels) between two or more samples using high density DNA microarrays. In Lockhart, a method of optimizing a set of probes for detection of a particular gene is disclosed. The probe optimization method involves first hybridizing the probes with their target nucleic acids alone and then hybridizing the probes with a high complexity, high concentration nucleic acid sample that does not contain the targets complementary to the probes (Lockhart, column 36, lines 30-36), and selecting those probes that show a strong hybridization signal with their target and little or no cross-hybridization with the high complexity sample as preferred probes for use in the high density arrays (Lockhart, column 36, lines 44-47). For selection of probes showing a strong hybridization signal with their target, Lockhart teaches that the probes are hybridized to a sample containing target nucleic acids having subsequences complementary to the oligonucleotide probes, and those probes are selected for which the difference in hybridization intensity between the probes and their respective mismatch controls exceeds a threshold hybridization intensity (see, e.g., Lockhart col. 37, lines 1-12). For selection of probes showing little or no cross-hybridization, Lockhart teaches that the probes can be hybridized with a nucleic acid sample that is not expected to contain sequences complementary to the probes, and those probes are selected for which both the probes and their mismatch controls show hybridization intensities below a threshold value (see, e.g., Lockhart col. 37, lines 13-27). Thus, in Lockhart, selection of probes that show a strong hybridization signal with their target and little or no cross-hybridization is achieved by evaluating a probe according to its amount of hybridization to the target sample, and comparing this amount to a threshold, and separately, evaluating the probe according to its amount of hybridization to the non-target sample, and comparing this latter amount to a second threshold value. Lockhart does not teach or suggest comparing directly the hybridization signal and cross-hybridization signal of the same probe, much less combining the hybridization signal and cross-hybridization signal of the same probe into a single quantity, e.g., a ratio, and using such a single quantity as a measure of the binding property of the probe.

As discussed above, Lo does not teach or suggest evaluating polynucleotide probes having predetermined nucleotide base sequences, i.e., polynucleotide probes comprising a

predetermined *nucleotide base sequence* complementary to at least a hybridizable portion of the target nucleotide sequence. In order for Lockhart to supplement what is missing in Lo for purpose of maintaining the Examiner's rejection, Lockhart would have to teach or suggest determining the sequence of Lo's recombinant probe molecule (which binds a "target sequence" in *N. gonorrhoeae* chromosomal DNA), and determining the respective binding properties, i.e., binding ratios, of the probe using a sample containing at least 75% the target of the probe and a high complexity sample. Since Lockhart teaches neither of these, Lockhart does not supply what is missing in Lo.

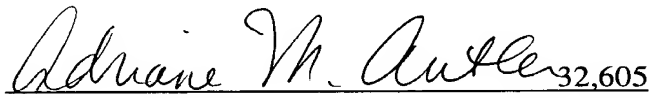
Therefore, Applicant respectfully requests that the rejection of claims 37, 39, 42, 92 and 94 under 35 U.S.C. § 103(a) based on Lo and the rejection of claims 61-63, 66, 74-75, and 84-85 under 35 U.S.C. § 103(a) based on Lo in view of Lockhart be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks into the file of the above-identified application. Applicant believes that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

Date: May 16, 2005



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